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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/725,188 | SIN ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *23-26 and 37-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,27-36 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-22, 27-36 and 45-47 filed on September 24, 2004 is acknowledged. Claims 23-26, 37-42 and 43-44 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The traversal is on the grounds that both Groups of claims are sufficiently related that an undue burden would no be placed upon the Examiner by maintaining both Groups of claims in one application. These arguments have been fully considered but are not found to be persuasive for the reasons below:

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct patented inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.01). In the instant situation, the inventions of Groups I-IV are drawn to distinct inventions which are separate products and methods capable of separate manufacture, use or sale as described in the previous Office Action.

Classification of the subject matter is merely one indication of the burdensome nature of the search. The literature search, particularly relevant in this art, is not co-extensive, because for example, Groups I and IV are drawn to different products. Groups II and III are drawn to different methods which require different method steps, parameters and endpoints. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

***Specification***

2. The specification is objected to for the following informalities: "Shiwanella" should be changed to "Shewanella" and "Flexinobactor" should be changed to "Flexibacter". The specification should be reviewed for these kinds of informalities and correction is required.

***Claim Objections***

3. Claims 1-22, 27-36 and 45-47 are objected for the following informality: The claims recite "AHMA" which should be changed to the adhesin protein of *Aeromonas hydrophila* at the first occurrence in the claims. Correction is required.

4. Claims 1-22, 27-36 and 45-47 are objected for the following informality: "Shiwanella" should be changed to "Shewanella" and "Flexinobactor" should be changed to "Flexibacter". The claims should be reviewed for these kinds of informalities and correction is required.

5. Claims 1-22, 27-36 and 45-47 are objected for the following informality: The claims recite " FP" which should be changed to *Ichthyophthirius multifiliis* at the first occurrence in the claims. Correction is required.

6. Claims 1-22, 27-36 and 45-47 are objected for the following informality: The names of the genus and species of an organism should be underlined or italicized. Correction is required.

7. Claims 27-36 are objected because they depend from a non-elected invention. Correction is required.

**Claim Rejections - 35 USC § 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-22, 27-36 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant protein major adhesin protein of *Aeromonas hydrophila* (AHMA) does not reasonably provide enablement for derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification defines the term "polypeptide derivative" as any polypeptides in which one or more amino acids have been replaced by different amino acids and which retains the function or activity of the polypeptide (page 6). The specification fails to provide a structure for the, derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila.*

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with

regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (page 315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the

interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record

establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use proteins that are derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila* in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the amino acid's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 5 and 12 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what Applicant intends by "comprises 1:2". Clarification is requested.

10. Claim 20 recites the limitation "constituent proteins". There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It should be noted that the Examiner is equating "nervous necrosis virus" as being the same as "guppy nervous necrosis virus".

11. Claim 1, 27-29 and 35-36 are rejected under 35 U.S.C. 102(a) as anticipated by Irianto et al *(Journal of Fish Diseases, February 2003, 26, 117-120).*

Claims 1, 27-29 and 35-36 are drawn to an oral vaccine comprising at least one recombinant protein AHMA, recombinant protein AHMA fragments and recombinant protein derivatives.

Irianto et al teach an oral vaccine composition comprising formalin-inactivated isolated from *Aeromomas hydrophila* and Freund's (see the Abstract and page 117). Irianto et al teach that the vaccine composition contained 2x107 bacterial cells $g^{-1}$ of the feed (page 117). The claim limitation "oral" is being viewed as a limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. Irianto et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

12. Claim 1-3, 5-6, 10 and 27-29 are rejected under 35 U.S.C. 102(b) as anticipated by Fang et al *(Journal of Fish Diseases, 2000, 23, 137-145).*

Claims 1-3, 5-6 and 10 are drawn to an oral vaccine comprising at least one recombinant protein AHMA, recombinant protein AHMA fragments and recombinant protein derivatives.

Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* and Freund's complete adjuvant (see the Abstract and page 139). Fang et al teach that the vaccine composition contained 150 $\mu g\ mL^{-1}$ of the protein (page 139). The claim limitation "oral" is being viewed as a limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. Fang et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 5-6,10-13, 15-16, 20-21, 27-36 and 45 are rejected under 35 U.S.C. 103(a) unpatentable over Wolf-Watz et al (*U.S. Patent No. 5,284,653 published February 8, 1994)* in view of Wang et al *(Fish Shellfish Immunol., Nov. 2002;13(5):337-50.*

Claims 1-3, 5-6, 10-13, 15-16, 20-21, 27-36 and 45 are drawn to an oral vaccine comprising at least one recombinant protein AHMA, recombinant protein AHMA fragments and recombinant protein derivatives further comprising recombinant protein FP.

Wolf-Watz et al teach a fish vaccine comprising live avirulent invasive bacteria (see the Title and the Abstract). Wolf-Watz et al teach that the invasive bacteria strains may be produced from known fish pathogens including *Aeromonas hydrophila* (column 5). Wolf-Watz et al teach that the invention contemplates that the mutant strain of the invention may carry DNA sequences coding for an antigenic determinants from other fish pathogens and is capable of expressing the sequence (column 6). Wolf-Watz et al teach that the invention contemplates vaccines comprising bacteria the carry multiple determinants from different pathogenic fish and capable of expressing hybrid (fusion) determinants (column 7). Wolf-Watz et al teach that viruses such as infectious

pancreatic necrosis virus and infectious hematopoietic necrosis virus may apart of the vaccine of the invention (column 6). Wolf-Watz et al teach that the bacteria of the invention contains $1x10^2$-$1x10^8$ bacteria/ml (column 8). Wolf-Watz et al teach that the vaccine of the invention can be added to fish feed (column 8).

Wolf-Watz et al do not teach the immobilization antigen repeat I of *Ichthyophythirius multifiliis* (FP).

Wang et al teach a vaccine composition comprising the immobilization antigen repeat I of *Ichthyophythirius* and Freund's incomplete adjuvant (see the Abstract). Wang et al teach that fish immunized with the FP antigen developed high titers of serum immobilized antibodies (see the Abstract). Wang et al teach that this study shows there is a clear role for the immobilization antigen repeat I of *Ichthyophythirius* in protection (see the Abstract). The claim limitation "recombinant" is being viewed as a process limitation.

It would be *prima facie* obvious at the time the invention was made to add the immobilization antigen repeat I of *Ichthyophythirius* as taught by Wang et al to the vaccine composition of Wolf-Watz et al because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila* and immobilization antigen repeat I of *Ichthyophythirius* would be effective in protecting against a broad spectrum of fish diseases.

14. Claims 1-6,10-16, 20-22, 27-36 and 45-47 are rejected under 35 U.S.C. 103(a) unpatentable over Wolf-Watz et al, Wang et al as set forth above for claims 1-3, 5-6,10-13, 15-16, 20-21, 27-36 and further in view of Morinigo et al *(Bulletin of the European Association of Fish Pathologists, Nov.2, 2002, Vol. 22, No.5, p. 298-303).*

Claims 22 and 46-47 are drawn to the oral vaccine of claim 1 further comprising bacterial antigens of killed bacteria selected from the group consisting of bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas florescens, Vibrio alginolyticus* and *Flexibacter columnaris.*

Wolf-Watz et al and Wang et al as combined above do not teach *Vibrio alginolyticus.*

Morinigo et al teach that a divalent vaccine composition comprising *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida.* Morinigo et al teach that the concentration of protein 800 mg $ml^{-1}$ (page 299).Morinigo et al teach that high protection was conferred by the divalent vaccine (page (302).

It would be *prima facie* obvious at the time the invention was made to add the *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens as taught by Morinigo et al to the vaccine composition of Wolf-Watz et al and Wang et al as combined above because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins

from *Aeromonas hydrophila,* immobilization antigen repeat I of *Ichthyophythirius,* and *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens would be effective in protecting against a broad spectrum of fish diseases.

15. Claims 1-6, 10-16, 20-22, 27-36 and 45-47 are rejected under 35 U.S.C. 103(a) unpatentable over Wolf-Watz et al, Wang et al and Morinigo et al as set forth above for claims 1-3, 5-6,10-13, 15-16, 20-22, 27-36 and 45-47 and further in view of Chen et al *(U.S. Patent No. 6,720, 001 B1, published April 13, 2004).*

Claims 4 and 14 are drawn to the oral vaccine of claim 1 further comprising palm oil.

Wolf-Watz et al, Wang et al and Morinigo et al as combined above do not teach palm oil.

Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). Chen et al teach that the compositions of the invention that contain organic oils such as palm oil are stable compositions (column 5).

It would be *prima facie* obvious at the time the invention was made to add the palm oil as taught by Chen et al to the vaccine composition of Wolf-Watz et al, Wang et al and Morinigo et al as combined above because Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). It would be expected barring evidence to the contrary

that a vaccine comprising palm oil would be effective stabilizing vaccines at improving delivery of polyfunctional active ingredients.

16. Claims 1-22, 27-36 and 45-47 are rejected under 35 U.S.C. 103(a) unpatentable over Wolf-Watz et al, Wang et al, Morinigo et al and Chen et al as set forth above for claims 1-6, 10-16, 20-22, 27-36 and 45-47 and further in view of Calanchi et al *(U.S. Patent No. 5,008,117, published April 16, 1991).*

Claims 7-9 and 17-19 are drawn are drawn to the oral vaccine of claim2 further mixed with a binding agent.

Wolf-Watz et al, Wang et al, Morinigo et al and Chen et al as combined above do not teach carboxymethylcellulose.

Calanchi et al teach that binding agents such as carboxymethylcellulose (column 3). Calanchi et al teach that binders are soluble in water and solvents (column 3). Calanchi et al teach that binders are often used to thicken the composition (column 4).

It would be *prima facie* obvious at the time the invention was made to add carboxymethylcellulose as taught by Calanchi et al to the vaccine composition of Wolf-Watz et al, Wang et al, Morinigo et al and Chen et al as combined above because Calanchi et al teach that binders are often used to thicken the composition and have the property of dispersing and dissolving quickly in water or aqueous vehicles (see the Abstract). It would be expected barring evidence to the contrary that a vaccine comprising binding agents such as carboxymethylcellulose would be effective at making

the components of the composition easily to disperse and dissolve quickly in water or aqueous vehicles.

***Status of Claims***

17. No claims allowed.

***Conclusion***

18. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
December 8, 2004

MARK NAVARRO
PRIMARY EXAMINER